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IN VITRO DIAGNOSTICS
The Basics

Introduction

Chances are at some point in your life you have utilized an In Vitro Diagnostic (IVD) device. An example could be a urine dipstick test to determine whether an individual is pregnant or a glucose monitor to regulate insulin intake. While these examples still play an important role within the IVD world, the field itself has evolved, and along with it, the response and regulatory authority of the FDA have evolved as well. According to the market research company Kalorama Information, the market value for In Vitro Diagnostics (IVD) was estimated to be $54.6 billion dollars in 2013 and is expected to rise to $75 billion dollars by 2020.[1,2] Furthermore, it was estimated that laboratory tests would play a role in 70% of health care decisions. According to our research, in 2015 the FDA approved 454 in vitro diagnostic devices either through the route of a premarket notification (251 approvals) or premarket approval submission (203 approvals). The purpose of this whitepaper will be to explore the role the FDA has played, and will continue to play, in regulating in vitro diagnostic devices. To do this we will examine the three groups of in vitro diagnostic devices: Analyte Specific Reagents (ASRs), Laboratory Developed Tests (LDTs) and In Vitro Diagnostic Devices (IVDs). We will examine the role IVDs have played in blurring the traditional lines between device and drug. Finally, the important role of IVDs in medicine in the 21st century will be discussed as health care shifts away from a model of "one size fits all."

Within the code of federal regulations, Part 809 of 21 CFR refers to in vitro diagnostic products for human use.[3] The FDA defines an in vitro diagnostic product as "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body." The term "in vitro" was explicitly referenced in the 1976 Medical Device Amendment to the Federal Food, Drug, and Cosmetic Act.[4] Under section 201(h) of the Federal Food, Drug, and Cosmetic Act an in vitro diagnostic falls under the classification of a medical device, and as

such regulation of these products fall under 21 CFR 812 (Investigational Device Exemption).[5] What separates an IVD device from other medical devices is the function of the device.[6] Whereas non-IVD devices function primarily in or on an individual, an IVD device involves products that collect, prepare, or examine specimens after they have been removed from the human body.

A 2013 report from Raman et al. listed a number of different roles IVDs play in health care:[7]

- Diagnosing disease or ruling out the presence of a disease
- Predicting the potential risk of eventually developing a disease or disorder
- Determining the likely course or outcomes of a disease
- Choosing the most effective and appropriate treatment
- Guiding disease management
- Monitoring response to treatment throughout care

Each of the three classes (ASRs, LDTs, and IVDs) have grown in complexity and evolved from their initial scope. As these have grown, the FDA has had to re-examine how these devices are regulated and enforced. To begin our discussion we will take a look at Analyte Specific Reagents. Initially these were considered to be building blocks for both laboratory and commercially available tests; however their role has grown from this initial distinction.

Analyte Specific Reagents

An ASR is defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" [21 CFR 864.4020(a)].[8] These reagents can be considered building blocks for either LDTs or IVDs. The Department of Health and Human Services published a final rule in 1997 that offered three regulations collectively referred to as the "ASR rule".[9]

1997 ASR Rule:

- The definition and classification of ASRs
- Restrictions on the sale, distribution, and use of ASRs
- Requirements for ASR labeling

Classification

As part of the ASR rule, the majority of ASRs were classified or reclassified as Class I medical devices and were considered exempt from the premarket notification requirements of section 510(k). There is a smaller group of ASRs that fall under the mantel of either Class II or Class III devices. An ASR would be regulated as a Class II device if it is used as a component in blood banking tests, and a Class II blood banking test can fall under one of two categories:

- **Tests required by the FDA that screen for diseases with a low potential for transmission.**
- **Tests used electively by blood blanks to screen for diseases that are likely to be transmitted to subsets of blood unit recipients known to be at a greater risk of infection.**

The elevation of an ASR to a Class III device would depend on the impact on public health. For example, tests that diagnose contagious and/or fatal diseases impacting the public health, such as with Human Immunodeficiency Virus type 1 (HIV-1) could fall under a Class III device. However in the 1997 publication, the authors note that a Class II or Class III ASR would most likely not be marketed independently from the tests themselves. And as ASRs are typically not marketed independently let us turn our attention to the sale, distribution, and use of ASRs.

Sale, Distribution, and Use

As part of the 1997 rule, the sale of ASRs are restricted "to those clinical laboratories regulated under Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity testing." And only physicians or other State authorized individuals can order a LDT developed using an ASR. Of note, the sale of an ASR to nonclinical laboratories does not fall under this umbrella. With the distribution of ASRs to both clinical and nonclinical settings, 21 CFR 809.10(e) establishes requirements for how an ASR should be labeled.

Labeling

When an ASR is classified as a Class I device, it must include the statement "Analyte Specific Reagent. Analytical and performance characteristics are not established." For Class II and Class III ASR devices the following statement must be included "Analyte Specific Reagent. Except as a component of the approved / cleared test (Name of approved/cleared test), analytical and performance characteristics are not established."

To assist with clearing up frequently asked questions regarding commercial ASRs the FDA issued a guidance in 2007.[10] One of the purposes of the 2007 guidance was to provide additional instruction for manufacturers to determine whether or not a particular product falls under the scope of the ASR rule. The guidance suggests notifying the FDA for clarification on the classification of a device and provides additional clarification to the characteristics that make up an ASR.

The focus within these characteristics should be on the word "single" and to re-visit the previously described notion that ASRs are "building blocks". The FDA views products that contain either multiple individual ASRs bundled together, or that include or require more than a single ASR to not be an ASR. Furthermore, reagents required to be used with a specific assay or instrument would not be considered an ASR but rather an IVD or IVD component. In either example, the FDA recommends a discussion to determine classification prior to monitoring.

Finally, within the released Guidance the FDA provides a number of recommendations based on the ASR rule and characteristics of the ASR as noted above.

Characteristics of an ASR

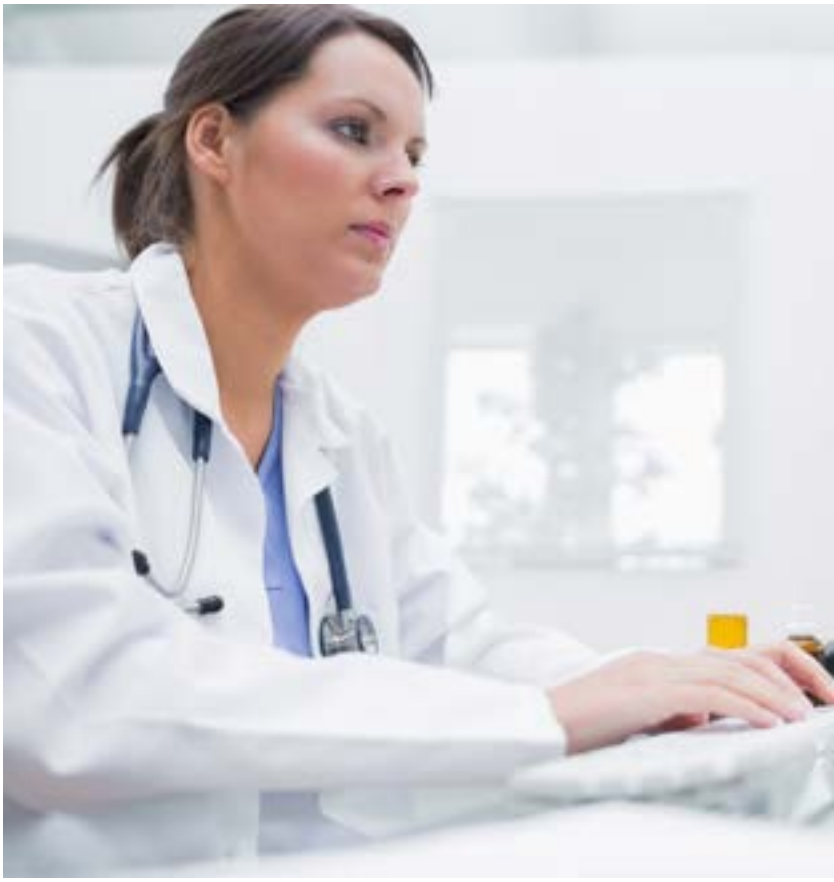
- Used to detect a single ligand or target. (e.g., protein, single nucleotide change, epitope)
- Not labeled with instructions for use or performance claims.
- Not promoted for use on specific designated instruments or in specific tests

These recommendations include the following:

- Manufacturers who wish to market multiple products as ASRs avoiding marketing in a manner that suggests that use of particular ASRs together will provide a particular effect, or that these devices should be used for a specific purpose.
- Manufacturers should not provide instructions for developing or performing an assay with an ASR, but should provide instruction for proper storage or handling.
- Manufacturers should not make claims to physicians or laboratories regarding analytical or clinical performance for ASRs.
- Manufacturers that want to market a product as an ASR should not assist with the development or validation of a LDT using its specific ASR.

Again the emphasis should be placed on the notion that ASRs are considered building blocks. Let us now move further up the totem pole of IVDs to examine LDTs.

Laboratory Developed Tests



The FDA defines a LDT as an IVD that is "intended for clinical use and [is] designed, manufactured and used within a single laboratory."[11] As with the distinction referenced previously with ASRs the focus should be on the word "single" as the FDA does not consider tests that are either manufactured or designed outside across multiple laboratories to be a LDT. And although a LDT is considered an IVD and thus falls under the same regulations as other IVDs, the FDA has historically exercised enforcement discretion with LDTs. Instead LDTs have fallen under the jurisdiction of the Center for Medicare and Medicaid Services (CMS). The jurisdiction of CMS over laboratory testing is a result of the Clinical Laboratories Improvements Amendment (CLIA). The first amendment in 1988 stated that "no person may solicit or accept materials derived from the human body for laboratory examination or other procedures unless there is in effect for the laboratory a certificate issued".[12] This amendment was passed in order to ensure quality standards regardless of where the laboratory testing occurred and since the initial amendment was approved in 1992 it has undergone three additional amendments in 1993, 1995, and 2003.[13] This level of oversight was considered appropriate as historically LDTs were used within a single institution using components already legally marketed for clinical use and were similar to standard diagnostic tests.[11] However, as the medical landscape has changed and testing has become more complex, the FDA has looked to exert additional control over these types of IVDs. In 2014 the FDA published a draft guidance regarding regulation of LDTs.[11] Prior to examining the reasoning behind this change in exertional control, let us first examine the types of LDTs that have traditionally fallen under CMS oversight.

The level of regulation under CLIA is dependent on the complexity of the test. A test can be of low complexity, moderate complexity, or high complexity. A low complexity test, or waived test, has a low amount of risk associated with it, either in the performance of the test or in the interpretation of results. Waived tests may also be eligible for over-the-counter or home use. An example of a waived test can include glucose monitoring systems.[14] Tests of moderate or high complexity can also be referred to as nonwaived tests. The complexity of a test is determined during the pre-market approval process and is based on scoring using a seven-point system with each point being scored from 1 to 3.[15,16] A total score of 12 or less would indicate moderate complexity and 12 or greater would be a test of high complexity. Manufacturers may also submit a Waiver Application to re-classify a nonwaived test to a waived test.

In demonstrating a test to be considered simple, the FDA provided a series of criteria to use when making this determination in a 2008 guidance document:[17]

- **Is a fully automated instrument or a unitized or self-contained test.**
- **Needs no technical or specialized training with respect to troubleshooting or interpretation of multiple or complex error codes.**
- **Needs no electronic or mechanical maintenance beyond simple tasks.**
- **Produces results that require no operator calibration, interpretation, or calculation.**
- **Produces results that are easy to determine, such as 'positive' or 'negative,' a direct readout of numerical values, the clear presence or absences of a line, or obvious color gradations.**
- **Provides instructions in the package insert for obtaining and shipping specimens for confirmation testing in cases where such testing is clinically advisable.**
- **Has test performance comparable to a traceable reference method as demonstrated by studies in which intended operators perform the test.**
- **Contains a quick reference instruction sheet that is written at no higher than a 7th grade reading level.**

Similar to ASRs the focus is on simple versus complex, and as LDTs have grown in complexity, the role the FDA has played in regulating these devices has grown. Within the 2014 regulatory guidance regarding the regulatory oversight of LDTs, the FDA noted that compliance with the CLIA regulations does not ensure the following items related to the tests.[11]

- Safety and effectiveness
- Clinical validity of the tests
- Does not require adverse event reporting or post-market safety monitoring
- No premarket review of performance data
- Does not require removal of unsafe devices from the market
- Does not assess quality manufacturing of devices
- Does not require informed consent for patients who participate in LDT clinical studies and does not establish procedures for the conduct of such studies
- Unsupported manufacturer claims
- Inadequate product labeling
- Lack of transparency
- Uneven playing field
- Threats to the scientific integrity of clinical trials
- No comprehensive listing of all LDTs currently being used

In 2015 the FDA published a report noting case study examples to support the need for additional oversight.[18] An example in this report involved a LDT for the treatment of HER2 type breast cancer. HER2-positive breast cancer is an aggressive cancer subtype that accounts for 10-20% of all invasive breast cancers.[19] While this is an aggressive subtype, it is treatable with drugs that target the growth factor receptor (HER2) that is found to be overexpressed in tumors driving cancer progression. However these drugs are not effective on other subtypes of breast cancer. As a result, a test to determine the cancer subtype is paramount for conscripting an effective therapy. While there are FDA approved tests on the market to determine the cancer subtype, the 2015 case study report noted a LDT that had “poor sensitivity” in determining an individual’s HER2 levels which could have an impact on both treatment and cancer progression.

Given this and other examples, the 2014 guidance proposed a change in policy of enforcement discretion with enforcement to be in line with the existing medical device classification system (Class I, II, or III). This classification is to be provided within two-years of the guidance being finalized. In the interim, discretion would continue to be enforced for LDTs that meet certain conditions listed below:

- Used solely for forensic (law enforcement) purpose
- Used in CLIA-certified, high-complexity histocompatibility laboratories for transplantation
    - Used for rare diseases
    - Manufactured and used within a single institution using legally marketed or general purpose instruments that are interpreted by a qualified laboratory professional.
- Unmet needs for tests without a FDA cleared or approved alternative

Conversely, enforcement discretion will be focused on the following LDTs:

- LDTs with the same intended use as a cleared or approved companion diagnostics (companion diagnostics will be discussed later in this Whitepaper)
- LDTs with the same intended use as an FDA-approved Class III medical devic
- Certain LDTs for determining the safety or efficacy of blood or blood products
- Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure, such as screening device for malignant cancers
- Diagnostic devices for certain infectious diseases with high-risk intended users

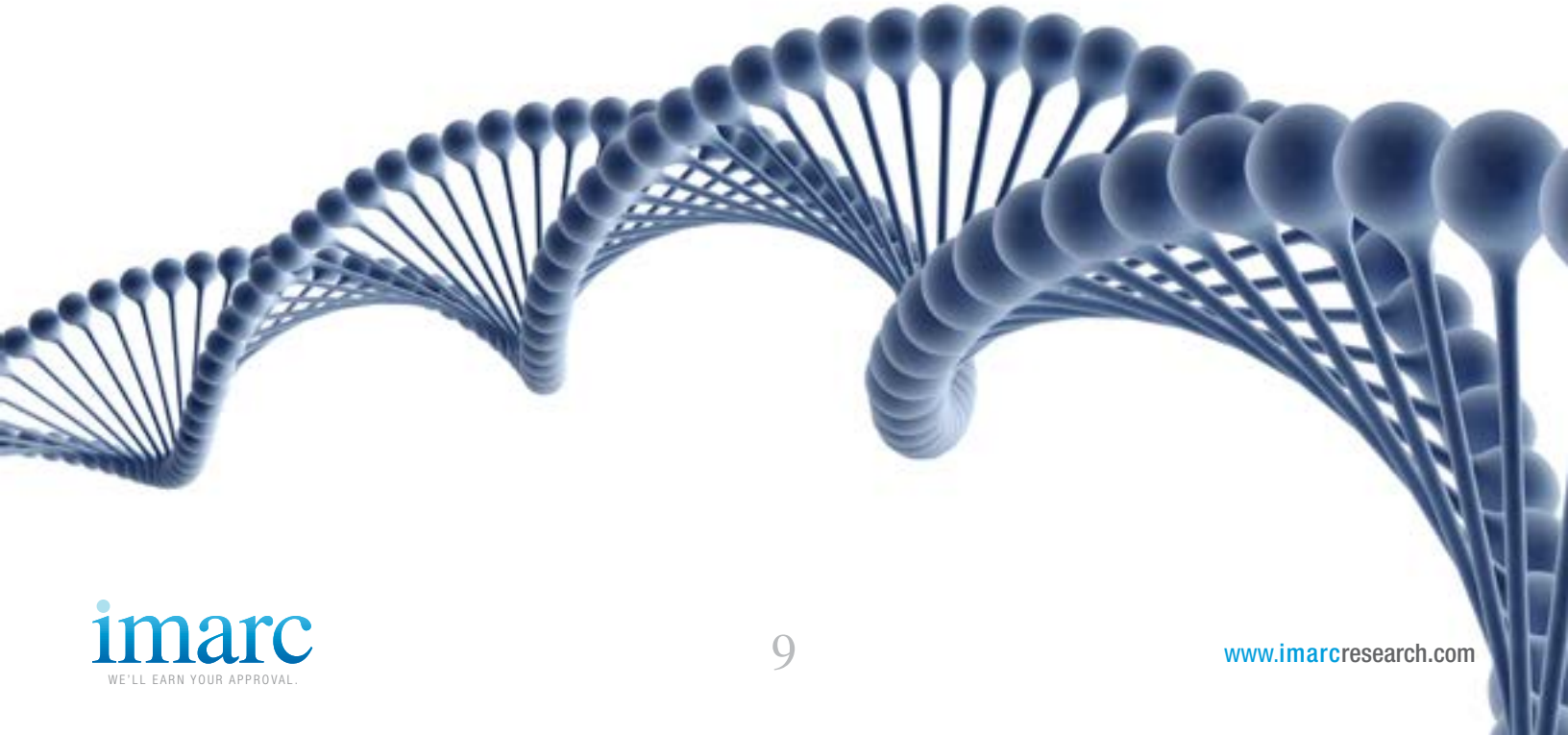
In other words regulatory discretion will begin with what the FDA views as the highest risk LDTs. Furthermore, the FDA notes that discretion would continue for all existing and premarket submissions through a 12-month period following the finalization of the draft guidance. However for the higher risk categories noted above, the FDA "intends to begin enforcing premarket review requirements immediately upon publication of this guidance document in final form."[11] With this in mind let us turn our attention to an example of a highly complex LDT that, prior to the 2014 guidance, had already made the transition to a distinct device category requiring both pre- and post-market device requirements, the In Vitro Diagnostic Multivariate Index Assay (IVDMIA).

An IVDMIA is a medical device that in some instances can also be classified as a LDT.

IVDMIA is defined as possessing two characteristics:[39]

- **Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a "classification," "score," " index," etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease**
- **Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.**

Devices under this classification can be used to either diagnose or predict disease risk and include such items as a gene expression profiling assay as a tool to determine breast cancer prognosis. Within a 2007 guidance regarding these devices the FDA echoed similar concerns brought forth in the 2014 guidance regarding LDTs, namely clinical validity and safety/effectiveness of the test. As a result, the FDA recommended that these types of devices be considered a distinct category requiring both pre-and post-market device requirements. The FDA does not consider devices that may process multiple variables to assist in healthcare interpretation to fall under this device category. To assist with this distinction, the FDA offered examples of devices that provided genotype or chromosomal copy numbers to fall outside this scope. However IVDMIA's offer an example of how LDTs have evolved in recent years and offers a bridge to the third class of IVDs,



In Vitro Diagnostic Devices

As we make the shift from the laboratory to commercially available tests our discussion of IVDs will focus on one area, companion diagnostics, as this particular arena provides evidence for the evolution of IVDs in the current medical field. However, prior to reviewing these two areas, let us first examine how diagnostics have traditionally fallen under FDA oversight. This oversight is similar to how other medical devices are treated, with a few unique features. Prior to submission, when a manufacturer is determining a device to have significant or nonsignificant risk, the FDA interprets potential serious risk for IVDs to include "misdiagnosis and/or error in treatment caused by inaccurate test results [and] would be considered a significant risk if the potential harm to the subject could be life-threatening, or could result in permanent impairment of a body function or permanent damage to the body structure."[20] 21 CFR 809.10 refers to the labeling requirements for in vitro diagnostic products and the FDA recommends that studies are designed "to support the proposed indications for use in the package insert and labeling."[21] IVDs that meet the criteria of exemption from IDE regulation also have a unique feature that non-individually identifiable leftover human specimens may be used in trials without the need for informed consent.[22] In a 2006 FDA Guidance, the FDA notes that leftover specimens offer certain characteristics that enable for human subject protection to be maintained in investigations that utilize leftover samples.

Leftover Specimen Characteristics:	• The samples are not identifiable • Results of the investigational test are not communicated or otherwise associated with the identified subject • New medical risks are not posed to subjects from whom the specimens were originally collected

Leftover samples provide investigators with features that can assist investigators in characterization of new IVD devices and feasibility studies, namely:

- **Quick determination for meeting inclusion criteria;**
- **Provide rare specimens for a faster completion of studies that would otherwise take much longer to complete.**

Of note, to be eligible, these samples must be also obtained as part of routine clinical care or other research and studies should still be reviewed by an IRB in accordance with 21 CFR 56.
With this in mind, let us now turn to the area mentioned previously: companion diagnostics.

Companion diagnostics

In vitro companion diagnostic devices are devices that "provide information… essential for the safe and effective use of a corresponding therapeutic product."[23] To be considered a companion device the FDA notes that it should both be "essential" and be used "for the safety and effectiveness" of a corresponding therapeutic product. An example of a companion diagnostic device would be a HER2 test, discussed earlier, that can be used to determine whether breast cancer treatment should include the class of drugs targeting the over expression of this growth factor receptor. The timing of the development of the therapeutic product and companion diagnostic product plays a role in how the FDA views the review and approval process of each. In these instances, the labeling of the device plays an important role. In a 2014 guidance the FDA provided additional information regarding both the submission process and labeling of devices.[23] In respect to the submission the FDA noted that "novel therapeutic products" would require approval of both [therapeutic product and companion diagnostic] in order to ensure safety and effectiveness. There is also a path for a therapeutic product to be approved separate from the companion diagnostic. For example, if the product in question involves treatment for a serious or life-threatening condition, the product without an alternative therapy may be approved prior to the approval or clearance of the companion diagnostic. It should also be noted that the manufacturer of a therapeutic product may differ from the manufacturer of the companion diagnostic or an existing IVD may be modified to partner with the therapeutic product. To account for these potential scenarios the FDA provided in the guidance a number of different ways this will be approached:[23]

- **The regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness.**
- **The FDA intends to issue approvals or an approval and clearance at the same time for a therapeutic product and companion diagnostic.**
- **For an IVD currently on the market, the FDA would consider an additional premarket submission for a new use of the device.**
- **New IVD companion diagnostic devices intended to be used in the same manner as an existing approved or cleared IVD companion diagnostic device will be reviewed under a PMA or a traditional 510(k) submission as appropriate**

When a therapeutic product is coupled to a companion diagnostic the labeling of each should be taken into account. Within the same guidance the FDA offers additional recommendations for the labeling of each.

Companion Diagnostic Labeling Recommendations:

Therapeutic Product

- The type of diagnostic test (if applicable) essential for monitoring the toxic or therapeutic efect.
- Information about the use of companion diagnostic.
- Should specify the use of an FDA approved or cleared companion diagnostic.
- Labeling should be updated if a companion diagnostic is cleared or approved after the therapeutic product.

Companion Diagnostic Product

- The name or class of therapeutic product for whom the device is approved or cleared.
- Labeling should be updated to reflect any new indications or therapeutic class.

IVDs In the 21st Century

What do the upcoming years held in store for In Vitro Diagnostic devices? As we have examined three groups of IVDs (Analyte Specific Reagents, Laboratory Developed Tests, and In Vitro Diagnostic Devices) a theme of evolution in the devices outside their initial scope should be evident. What should also be evident is that the response from FDA in recent years has contributed to this evolution. The separation between laboratory versus commercial tests has become smaller, and the ability to couple a therapeutic product to an IVD has grown. Additionally, advancements in technology have led to offshoots of these groups (i.e. IVDMIA) that have further led to delineation, and prompted additional evaluation of the role of FDA. Another example of this is the rise in mobile medical apps in use in portable devices such as phones or tablets. This has led to the FDA responding to what apps would require regulation.[24] Still yet another example is the increase in direct to consumer genetic tests. Within this field, the FDA has evaluated the information being disseminated and this has resulted in warning letters issued to some manufacturers.[25,26] The issuance of these letters has also led to a response from the scientific community.[27]

This last example offers a gateway into the area of personalized medicine and the role IVDs will play in this arena. Kalorama Information identified the role of IVDs in personalized medicine as number 2 in the top 5 trends to watch in 2016.[28] During his 2015 State of the Union Speech, President Obama unveiled his vision of the Precision Medicine Initiative.[29] This initiative proposed to bring three government agencies together, the Food and Drug Administration (FDA), the National Institute of Health (NIH), and the Office of the National Coordinator for Health Information Technology (ONC) in an effort to move away from a "one-size-fits-all" approach in treating disease. As a response to this initiative the FDA commissioner at the time, Margaret Hamburg, published remarks she gave at a meeting outlining some of the challenges offered by personalized medicine.[30] One example offered in her remarks is the use of Next Generation Sequencing devices in personalized medicine. First approved in 2013, these devices can be used to validate and identify potential genomic variants.[31] However these devices also generate a large amount of data which can make this validation and identification difficult. And with the amount of data generated, studies limited

studies limited to only a single variant or single test. to validate can result in a very large amount of unused data. A blog published by the FDA in September highlighted some of these challenges and a public workshop in November 2015 attempted to work through these challenges.[32,33] And on 15 December 2015, the FDA launched PrecisionFDA.[34] This site is "a cloud-based portal that will allow scientists from industry, academia, government and other partners to come together to foster innovation and develop the science behind next-generation sequencing and help us design treatments tailored to a person's individual genetic blueprint."[35] And while this site will not serve in a regulatory role, it will be used to help and inform regulatory decisions going forward. Finally, on 25 February 2015, the White House held a Precision Medicine Initiative summit to follow-up on where things stood one year later.[36] Within this announcement the White House noted the passing of recent legislation providing funds towards this cause and provided a series of actions that have taken place in the preceding year.[37] Of the additional actions, one of note has to do with the Department of Health and Human Services Office for Civil Rights issuing guidance on individuals' rights under the Health Insurance Portability and Accountability Act (HIPAA).[38]

And as this one-year summary illustrates this is a rapidly accelerating convergence of health care, research, companies, and information available to the consumer. As with the evolution of both in vitro diagnostics and the regulation of these devices it should be clear that these devices will continue to play an increasingly important role in the health care field and be at the center of this confluence. And with this important role comes the need for continued research, development, and oversight of trials for these devices in order to ensure that the promises they offer are delivered.

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Michael joined IMARC in February 2014 and has monitored studies investigating treatments for thoracic aneurysms, ulcers, internal iliac artery patency, and acute MI diagnostics. His diverse background in working in a wide array of scientific fields, large datasets, and utilizing innovative approaches to tackle complex diseases has aided him in tackling new projects and providing fresh insight when monitoring clinical studies. His ability to distill complex information into simple concepts allows him to work well with sites to follow challenging protocols. In addition, he strives to maintain open communication between sites and sponsors in order to leverage the needs of both while maintaining perspective on additional non-study related responsibilities of each. When he is not monitoring clinical trials, Michael enjoys staying current on new trends in medical devices, personalized medicine, and FDA Guidances.

Michael received both his Masters Degree and Undergraduate Degree in Biology at John Carroll University in University Heights, Ohio.

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